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MICHAEL P. MORRIS
BOEHRINGER INGELHEIM USA CORPORATION
900 RIDGEBURY RD
P O BOX 368
RIDGEFIELD, CT 06877-0368

EXAMINER	
HAGHIGHATIAN, MINA	

ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
11/17/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTO.e-Office.rdg@boehringer-ingelheim.com

Office Action Summary	Application No.	Applicant(s)	
	10/735,959	DRECHSEL ET AL.	
	Examiner	Art Unit	
	Mina Haghighatian	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,16,18-20,22-31,38-66,68 and 70-95* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,16,18-20,22-31,38-66,68 and 70-95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of the Amendments and Remarks filed on 08/10/09. Claims 1-14, 16, 18-19, 22-31, 38-39, 41, 44-66, 68, 70, 72-95 have been amended and no claims have been cancelled or newly added. Accordingly, claims **1-14, 16, 18-20, 22-31, 38-66, 68 and 70-95** remain pending.

Rejections and/or objections not reiterated from the previous Office Action are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-14, 16, 18-20, 22-31, 50, 53-66, 68, 70-80 and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freund et al (DE 19653969 as evidenced by US 2001/0008632) in view of Freund et al (WO9701329 as evidenced by US 6,491,897).

Freund et al '632 teach pharmaceutical preparations in the form of **aqueous solutions** for the production of propellant-free aerosols for inhalation for the therapy of obstructive lung diseases. Pharmaceuticals intended for inhalation are dissolved in an aqueous or ethanolic solution or a **solvent mixture of ethanol and water**. The amount of dissolved pharmaceutical in the preparation is **between 0.001 and 30%,** and preferably between 0.05 and 3%. All substances which are suitable for application by inhalation and which are soluble in the specified solvent can be used as pharmaceuticals in the new preparation. Of especial interest are betamimetics, anticholinergics, antiallergic, antihistamines and steroids, as well as combinations of these active ingredients (sections [0001] to [0007]).

Freund et al '632 teaches that addition of an effective amount of a complexing agent, such as, **EDTA, citric acid, ascorbic acid and their salts**, and more especially disodium salt of ethylenediaminetetraacetic acid, eradicates the problem of spray anomalies. The effective quantity of complexing agent Na-EDTA is between 10 and 100 mg/100 ml. Also if necessary, ethanol can be added to increase solubility up to 70% by volume. Other adjuvants such as preservatives, especially benzalkonium chloride can be added in amounts of between 8 and 12 mg/100 ml (sections [0009] to [0013]).

Freund et al '632 discloses a list of compounds which can be used as active ingredients, singly or in combination, in the aqueous pharmaceutical preparation. In individual cases, it may be required to add a higher quantity of ethanol or a solution mediator to improve solubility. The list includes; **tiotropium bromide**, budesonide, beclomethasone, disodium cromoglycate, etc. The solutions are set to a pH of 3.2 to 3.4 with 0.1 or 1 N **HCL** in 100 ml of finished preparation (see sections [0014] to [0046] and [0055]). Freund et al '632 does not specifically disclose pH levels of 2.0 to 3.0.

Freund et al '897 teach a stable ethanolic solution of budesonide suitable for nebulization (see abstract). The formulation may further comprise other active agents such as tiotropium bromide (col. 2, lines 6-49). The formulation preferably has a pH of from 2 to 7, adjusted by the amount of an acid such as hydrochloride acid (see col. 2, lines 60-67). In a preferred embodiment, the formulations comprise a quantity of a complexing agent, preferably EDTA, from about 0.1 to about 3 mg/100 mL (col. 3, lines 1-15)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the formulations of Freund et al '632 comprising tiotropium, solvent, an acid, EDTA and other additives such as benzalkonium chloride by implementing the teachings of Freund et al '897 on lower amount of EDTA and lower pH levels, with a reasonable expectation of successfully preparing safe and stable formulations. In another word, the claims would have been obvious because the

technique for improving a particular product was part of the ordinary capabilities of a person of ordinary skill in the art, in view of the teaching of the technique for improvement in other situations. In this situation the improvement is lowering pH levels. One of ordinary skill is well aware that by adjusting the concentration of the acid the pH levels would be adjusted. Freund et al '632 teach that low pH levels are suitable for the said formulations, and one could further lower the pH levels to test for stability.

Claims 38-49, 51-52, 81-92, 94 and 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freund et al in view of Freund et al and further in view of Weston et al (WO 9114468).

Freund et al and Freund et al discussed above, lack specific teachings on the inhalation device.

Weston et al discloses a metered dose inhaler which incorporates metering means for metering a quantity of fluid, and the atomizing means is provided by a mechanical break up device through which the metered quantity of fluid is passed to atomise it when it is subject to said increase in pressure (page 7, lines 5-9). For dispensing a spray of an aqueous solution of a medicament for inhalation into lungs, the droplet size is desirably less than 10 micrometers, typically 2 to 6 micrometers.

Weston also discloses that very high pressures can be generated in the pump cylinder or pressure and nozzle orifice diameters can be used, for example up to 100 micrometers, typically greater than 30 to 50 micrometers. The preferred pressures are

from 50 to 400 bar, and more preferably from 100 to 350 bar with nozzle orifice of from 1 to 12 micrometers (page 12, lines 1-32).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have utilized the preparation of Freund et al., by incorporating it in a device suitable for such preparations and because it is made simpler in design and cheaper to produce and suited to its function, as taught by Weston et al.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims **1-14, 16, 18-20, 22-31, 38-66, 68 and 70-95** are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of copending Application No. 11/068,134 (US 20050147564). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims would have been anticipated by the reference claims. The claims of the co-pending application are drawn to a formulation comprising a first active agent comprising a tiotropium salt in a concentration range of between 0.0005% and 5% by weight, a steroid, a solvent such as water or ethanol and a preservative, wherein the formulation has a pH of from 2.0 to 3.5. The claims of instant application are drawn to a similar preparation. The difference is that the steroid is not required.

This is a provisional obviousness-type double patenting rejection.

Claims **1-14, 16, 18-20, 22-31, 38-66, 68 and 70-95** are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of copending Application No. 10/392,558 (US 20040019073). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims would have been anticipated by the reference claims. The claims of the co-pending application are drawn to a formulation comprising a tiotropium salt in a concentration range of between 0.01 and 0.06 g per 100 ml of formulation, a solvent such as water and a preservative, wherein the formulation has a pH of from 2.7 to 3.1. The claims of instant application are drawn to a similar preparation. The difference is that the concentration range of tiotropium is slightly different.

This is a provisional obviousness-type double patenting rejection.

Claims **1-6, 38, 53-58 and 81** are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of copending Application No. 12/201,149 (US 20090088408). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims would have been anticipated by the reference claims. The claims of the co-pending application are drawn to a formulation comprising a first active agent comprising a tiotropium salt, a steroid, a betamimetic and acceptable excipients and carrier. The claims of instant application are drawn to a similar preparation. The difference is that the steroid and the betamimetic are not required. The instant claims also require EDTA and water or ethanol/water as the solvent. However the claims of the reference employ the open language of "comprising" which allows for the other components to be included.

This is a provisional obviousness-type double patenting rejection.

Claims **1-14, 16, 18-20, 22-31, 38-66, 68 and 70-95** are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of copending Application No. 11/006,940 (US 20050148562). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims would have been obvious over the reference claims. Instant claims are drawn to formulations comprising an anticholinergic, preferably tiotropium

and a second active agent such as a steroid. Formulations can be in a solution form and thus require a solvent. The preferred pH rang is from 2 to 7 (see e.g. claims 114 and 229). The claims of instant application are drawn to a similar preparation. The difference is that the second active agent such as steroid is not required.

This is a provisional obviousness-type double patenting rejection.

Response to Arguments

Applicant's arguments filed 08/10/09 have been fully considered but they are not persuasive.

Applicant argues that the previously submitted evidence of the unexpected advantage and nonobviousness, demonstrates the nexus between the combination of lower EDTA-content with lower pH and the advantageous absence of spray anomalies. Applicant asserts that Table 1 of Freund '632 relates to ipratropium bromide solutions at 3.4 pH and not tiotropium salt solutions at claimed pH range. This is not persuasive because tiotropium and ipratropium are closely related compounds and one would expect them to behave the same under the same conditions or at least not the opposite.

Applicant argues that "one of ordinary skill in the art observing the trend in Table 1 of Freund '632 could not have expected from the reference that a tiotropium bromide solution at pH 2.5 to 3.0 and a lower EDTA amount would lead to less occurrence of spray anomalies. This is correct however it is not convincing because as mentioned before, the data provided does not support the unexpected result as claimed by Applicant.

The data does not show criticality or unexpected results because one can not make any conclusion about the effect of low pH and low EDTA levels on spray anomalies. At pH levels of from 2.7 to 3.0, the number of sprays at 0-50mg/100g NaEDTA are not consistent with any conclusion. For example, at pH of 2.7 and 2.8, the formulations comprising 10 mg of NaEDTA showed 0 number of sprays with deviation, but at pH of 3.0, the formulations comprising 25mg showed 0 number of sprays with deviation. The results for the pH level of 2.7 (at 10 and 25mg) were very similar to those with a pH of 3.2, which is outside of Applicant's optimum pH level. On the other hand the number of sprays with deviation for the formulations at pH level of 2.8 and 25mg were the same as those for the pH of 3.1 and 50 mg and pH of 3.2 and 50 mg. In fact a formulation with a pH of 3.2 at 25 mg EDTA has a lower spray deviation levels (2.5%) than the formulation with pH of 2.8 and 25 mg EDTA (5.0%). Thus Applicants assertion that "An improvement of spray quality at lower pH values (2.7-3.0) in combination with lower NaEDTA concentrations (10 and 25 mg) is observed" is not found persuasive.

Applicant argues that "At each given pH value where a range of Na-EDTA content is tested, the number of actuations having deviations is always less for the embodiments within the claimed scope (i.e. at 10 or 25 mg/100 ml Na-EDTA) compared to embodiments at 50 mg/100 ml Na-EDTA. While this statement may be correct, this is not sufficient to support criticality of the levels. The criticality of a specific range is shown compared to the ranges outside of the claimed ranges. Here, the 0 and low levels of anomalies are observed with pH levels outside of the claimed levels and amounts outside of the claimed Na-EDTA amounts. For example, at pH levels of 3.2

and 50 mg/100ml Na-EDTA (both of which are outside of the claimed range), the percent of anomalies is the same as that for pH of 2.8 and 25 mg/100 ml (both show anomaly of 5%). Furthermore, it is noted that Applicant's statement is also true for the pH ranges outside of the claimed range. At pH levels of 3.1 and 3.2 the percent anomaly increases as the amount of Na-EDTA increases. For pH level of 2.8 there are no data at 50mg and at 0 amount of Na-EDTA, there are no anomalies for 2.7 and 3.3. Equally data is inconclusive for other ranges. For example, an amount of 25 mg of Na-EDTA produces 2.6% anomaly at pH of 2.7, 5.0% at pH of 2.8, 0% at pH of 3.0 and 2.5% at pHs of 3.1 and 3.2. Thus Examiner is unable to make any conclusions from the data based on Applicant's assertion of unexpected results for the specific pH range of 2.5 to 3.0.

Additionally, not only the submitted data does not support Applicant's assertion of unexpected results for the claimed range, there is no side-by-side data comparing the instant claims to that of the closest prior art.

Applicant also argues that "Freund '632 does not disclose general conditions encompassing the claimed compositions since one of ordinary skill in the art would have to modify Freund '632 outside its disclosed pH range to arrive at the claimed invention".

This is not persuasive because Freund teaches the formulations can have pH of from 3.2 to 3.4. It is considered that a pH of 3.2 is not patentably distinguished form a pH of 3.0 absent any criticality. In another words, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or

workable ranges by routine experimentation. **In re Aller, 220 F. 2d 454, 105 USPQ 233 (CCPA 1955).**

Rejections under provisional Double Patenting are maintained until such time as allowance.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mina Haghighatian whose telephone number is (571)272-0615. The examiner can normally be reached on core office hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mina Haghighatian/

Mina Haghighatian
Primary Examiner
Art Unit 1616